APPENDIX "A"

Copy of a "Declaration of Dr. Malcolm John Stoker Pursuant to 37 CFR § 1.132," dated July 31, 2006.

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PATENT & TRADEMARK OFFICE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Erik H.F. Wong et al.
Serial No.: 10/758,864
Filed: January 16, 2004
Title: METHOD OF TREATING PERIPHERAL NEUROPATHY
Group Art Unit: 1614
Examiner: Phyllis G. Spivack
Attorney Docket No.: 30744/6248.11

DECLARATION OF DR. MALCOLM JOHN STOKER PURSUANT TO 37 CFR §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

I, Malcolm John Stoker, hereby declare that:

1. I have reviewed the above-captioned patent application and am familiar with the subject matter disclosed therein.

2. I have reviewed and am familiar with a U.S. Patent and Trademark Office (USPTO) official action dated April 6, 2006, in which the USPTO commented on the application.

3. On June 26, 2006, I participated in an interview at the USPTO with an attorney prosecuting this application (Sandip H. Patel), one of my colleagues (Keith S. Ruddock), and the examiner responsible for reviewing the application (Phyllis G. Spivack).

4. My education experience is as follows:

 (a) I received my Bachelor of Science degree (with Special Honours) in Psychology with Statistics from the University of London in 1969.

 (b) I received my Master of Science degree in Clinical Psychology from the University of Leeds in 1971.

(c) I received my Master of Science degree in Experimental Pharmacology from the University of Bradford in 1976.

(d) I received my Ph.D. in Pharmacology from the University of Manchester in 1982.

5. My professional experience is as follows:

(a) From 1971 to 1980, I held Clinical Psychologist positions at Middlewood Hospital, Sheffield, and then with Kirklees Area Health Authority, both of which are located in the United Kingdom (U.K.).

(b) From 1982 to March of 2002, I held Clinical Research Manager or Director positions at the following companies:

(i) Astra Pharmaceuticals,

(ii) Beecham Pharmaceuticals,

(iii) SmithKline Beecham,

(iv) Marion Merrell Dow,

(v) Solvay Duphar, and

(vi) Solvay Pharmaceuticals.

(c) Since March of 2002, I have been employed by Pfizer Limited (hereinafter "Pfizer") in Sandwich, Kent (U.K.), as a Senior Director in the Neuroscience and Pain therapeutic areas.

(d) I have been an Associate Fellow of the British Psychological Society since 1973, and a Chartered Psychologist since 1988..

6. Based on my education and professional experiences, I am qualified to provide the comments set forth herein regarding the subject matter of the above-captioned application.

7. The following sub-paragraphs describe peripheral neuropathy:

(a) The peripheral nervous system consists of motor and sensory nerves that connect the brain and spinal cord (i.e., the central nervous system) to every other part of the body—i.e., it consists of the nerves outside of the central nervous system.

(b) "Peripheral neuropathy" is a term that describes a disorder of, or damage to, the peripheral nervous system. The disorder or damage may affect a single nerve (mononeuropathy) or one or more nerves simultaneously

(polyneuropathy). *See generally*, The Merck Manual of Diagnosis and Therapy, 16th ed., p. 1518 (Merck Research Labs., Rahway, NJ, 1992) (copy attached as Exhibit "A").

(c) Although a variety of events may cause damage to the peripheral nervous system, these events generally produce common symptoms indicative of peripheral neuropathy. These symptoms include, for example, pain, weakness, sensory loss, and tingling sensations. *See generally*, The Merck Manual of Diagnosis and Therapy, 16th ed., p. 1518 (Merck Research Labs., Rahway, NJ, 1992) (Exhibit "A"). Consequently, peripheral neuropathy is art-recognized and diagnosed as "a symptom complex rather than a disease entity." Ibid at 1520 (Exhibit "A").

(d) Treatment of a symptom complex, such as peripheral neuropathy, may be accomplished by alleviating or otherwise controlling one or more symptoms. This treatment is consistent with the teachings in the specification, which state, for example:

> Treatment or prevention of above disorders involves the administration of reboxetine in a manner and form that result in a reduction in the symptoms of the disease or disorder.

Specification at p. 29, lines 12-14. Although the foregoing statement from the specification refers to treatment with (racemic) reboxetine, the skilled artisan, having considered the application's teachings as a whole, would have readily understood that the statement is applicable to treatments with (S,S) reboxetine as well.

8. Individual peripheral neuropathies are diagnosed by recognition of a distinguishing set of symptoms.

(a) Peripheral neuropathy caused by diabetes is the most common form and is generally referred to as diabetic peripheral neuropathy (DPN). DPN is a representative polyneuropathy pain model.

(b) Post herpetic neuralgia (PHN) is another peripheral neuropathy and classically presents after a patient has suffered a Herpes Zoster infection. PHN is a representative mononeuropathy pain model.

(c) PHN is easily diagnosed because it has a symptom profile that includes many of the common symptoms indicative of peripheral neuropathy, including pain. This symptom profile makes PHN useful for clinical study of painful

peripheral neuropathies, and also qualifies PHN as a representative disorder to study when considering the effective treatment of painful peripheral neuropathies.

(d) Both PHN and DPN are well-known neuropathic pain syndromes.

9. With approval from the European Medicines Evaluation Agency (EMEA, London), Pfizer commercially manufactures pregabalin[1] capsules for the treatment of peripheral neuropathic pain in adults, and sells those capsules throughout the European Union under the product name "LYRICA®."

10. In bringing the LYRICA® product to market, Pfizer (and Warner-Lambert Company, which Pfizer acquired in 2000) demonstrated through a program of clinical studies that pregabalin is safe and effective in treating patients suffering from PHN and in treating patients suffering from DPN. *See* European Summary of Product Characteristics (SPC) for the LYRICA® product at § 5.1 at p. 11 (copy attached as Exhibit "B")[2]. Based on results Pfizer obtained through this program, the EMEA provided Pfizer with its approval to sell the LYRICA® product throughout the European Union for the treatment of peripheral neuropathic pain—not simply the treatment of PHN and DPN. Consequently, this agency has recognized that demonstrated efficacy in treating patients suffering from PHN and demonstrated efficacy in treating patients suffering from DPN are indicative of efficacy in treating patients suffering from pain associated with peripheral neuropathy.[3]

11. The program of clinical studies Warner-Lambert Company (which Pfizer acquired in 2000) undertook to obtain approval of the LYRICA® product—i.e., beginning clinical studies in 1998 with patients suffering from PHN or DPN—is consistent with a program a pharmaceutical company would undertake in seeking to obtain approval of a product for the treatment of peripheral neuropathies because, as stated in paragraph 8(c), above, PHN is useful for clinical study of painful peripheral

[1] Pregabalin is the *S* enantiomer of 3-(aminoethyl)-5-methylhexanoic acid. Pregabalin is an anticonvulsant that is structurally and pharmacologically related to gabapentin. Gabapentin has been approved in many European member states for the treatment of neuropathic pain, and is commercially available under the product name "NEURONTIN®."

[2] According to this SPC, "[p]regabalin binds to an auxiliary subunit (α_2-δ protein) of voltage-gated calcium channels in the central nervous system, potently displacing [^{3}H]-gabapentin." Exhibit B at p. 11 (§ 5.1).

[3] Additional clinical studies with the LYRICA® product are on-going relative to other peripheral neuropathies, such as, for example, neuropathic pain induced by multiple sclerosis (Exhibit "C"), neuropathic pain subsequent to trauma (Exhibit "D"), neuropathic pain induced by HIV (Exhibit "E"), and neuropathic pain associated with lumbo-sacral radiculopathy (Exhibit "F").

neuropathies, and its symptom profile qualifies PHN as a representative disorder to study when considering the effective treatment of painful peripheral neuropathies. Moreover, both PHN and DPN are well-known neuropathic pain syndromes. *See* ¶ 8(d), above.

12. I have reviewed a copy of, and am familiar with the subject matter described in the "Statutory Declaration" dated 23rd September, 2005, of Dr. Sian Louise Ratcliffe, which I understand was submitted to the USPTO in connection with the above-captioned patent application. Dr. Ratcliffe is a colleague of mine and we are commonly-employed by Pfizer. The subject matter of Dr. Ratcliffe's Declaration relates to an analysis of certain results obtained in a clinical study (namely, Pfizer Study A6061001) performed by Pfizer. In the paragraphs below, I describe that study in additional detail and provide additional analyses regarding the results.

13. Pfizer studied (S,S) reboxetine (in Pfizer Study Protocol A6061001) in a five-week randomized, double-blind, placebo-controlled, multi-center study with patients suffering from PHN who were gabapentin treatment failures. These patients also are referred to hereinafter as "subjects." The following sub-paragraphs describe the study:

(a) Fifty-two centers in the United States enrolled subjects into the study.

(b) Those subjects showing no or minimal improvement on the Patient Global Impression of Change (PGIC)[4] after treatment with gabapentin (1800 mg/day), or who were unable to tolerate gabapentin (1800 mg/day) were randomized to receive a placebo or (S,S) reboxetine for a period of five weeks.

(c) The randomization was stratified by age into those aged less than 75 years (non-elderly) and those aged 75 years or more (elderly).

(d) Those subjects receiving (S,S) reboxetine received (S,S) reboxetine doses that escalated over a two-week period to a maximum of 6 mg/day for non-elderly subjects, and to a maximum of 4 mg/day for elderly subjects.

(e) A total of 206 subjects were randomized to treatment and are included in an intent-to-treat (ITT) population. A total of 146 subjects were correctly randomized, adhered closely to the protocol treatment regimen, completed baseline and week-5 assessments and, therefore, are included in the per

[4] Patient Global Impression of Change (PGIC) is a patient-reported periodic assessment of their perception of change (if any) in their condition.

protocol (PP) population. The primary population for analysis is the ITT population.

(f) Baseline patient characteristics of the subjects were similar across treatment groups. For example, approximately 88% of the subjects were white, 48% were female, and the mean age of the subjects was 68.5 years. Sixty-seven percent of patients who were randomized subsequent to the gabapentin treatment phase fulfilled criteria for therapeutic failure with gabapentin, while the remaining 33% had failed to tolerate gabapentin (1800 mg/day).

14. Results of the study protocol described in Dr. Ratcliffe's "Statutory Declaration" demonstrate that (S,S) reboxetine is effective to treat pain associated with PHN (a peripheral neuropathy). *See, e.g.*, the Ratcliffe declaration at p. 12 (Appendix 5) (stating that "ssRBX [(S,S) reboxetine] was clearly efficacious in the treatment of PHN in subjects who are GBP [gabapentin] treatment failures").

15. Additional results of the study protocol demonstrating this efficacy are summarized in the following sub-paragraphs:

(a) According to an ITT population Last Observation Carry Forward (LOCF)[5] analysis, the difference in the adjusted mean change (from baseline to week five) in weekly average pain score between (S,S) reboxetine and the placebo (i.e., (S,S) reboxetine minus placebo) was –0.82 ($P < 0.001$) with a corresponding 90% confidence interval (90% CI) of -1.24, -0.41. For the per protocol analysis, the difference in adjusted mean changes was -1.15 (90% CI: -1.63, -0.67).

(b) The (S,S) reboxetine-placebo difference for pain diary data was highly and statistically significant across both ITT-LOCF and per-protocol data-sets. The point estimates of the (S,S) reboxetine-placebo difference were -0.82 (ITT-LOCF) and -1.15 (per protocol). This study was powered for a delta of -1.0 to accommodate the treatment-resistant nature of the study population.

(c) The robustness of these results is underscored by the results obtained for the secondary outcome measure, including responder rates and PGIC, which support those obtained for the primary outcome measure. The foregoing results from Pfizer Study Protocol A6061001 are evidence that (S,S)

[5] Last Observation Carry Forward (LOCF) is an analysis in which observations are carried forward to the last time point for patients who dropped out.

reboxetine is effective to treat PHN, a peripheral neuropathy, in patients who have failed to respond to an adequate course of treatment with gabapentin.

16. On the basis of the favorable efficacy and adverse events results Pfizer obtained in Pfizer Study Protocol A6061001, Pfizer has initiated a clinical study in patients suffering from pain associated with DPN.

17. Because PHN is a representative disorder to study when considering the effective treatment of painful peripheral neuropathy (see ¶ 8(c) and 9, above), It is reasonable to conclude that (S,S) reboxetine would be effective in the general treatment of painful peripheral neuropathy for at least the following reasons:

(a) PHN is easily diagnosed because it has a symptom profile that includes many of the common symptoms indicative of peripheral neuropathy, including pain. This symptom profile makes PHN useful for clinical study of painful peripheral neuropathies, and also qualifies PHN as a representative disorder to study when considering the effective treatment of painful peripheral neuropathies. *See* ¶ 8(c), above.

(b) The results of Pfizer Study Protocol A6061001 substantiate the efficacy of (S,S) reboxetine in the treatment of PHN, a peripheral neuropathy.

(c) A regulatory authority (namely the EMEA) has recognized that demonstrated efficacy in treating patients suffering from PHN and demonstrated efficacy in treating patients suffering from DPN are indicative of efficacy in treating patients suffering from pain associated with peripheral neuropathy. *See* ¶ 10, above.

18. I understand that the present application relates to a method of treating peripheral neuropathy using (S,S) reboxetine, or a pharmaceutically acceptable salt thereof. I also understand that the present application is based on the patent applicants' finding that (S,S) reboxetine is a highly selective noradrenaline (norepinephrine) reuptake inhibitor, which is devoid of effects on other neurotransmitters.

19. The Applicants' having found (and substantiated) that a compound ((S,S) reboxetine) with a mechanism of action involving highly selective noradrenaline (norepinephrine) reuptake inhibitory activity, and which is devoid of effects on other neurotransmitters, has efficacy in the treatment of PHN, a peripheral neuropathy, the known efficacy of anticonvulsants (e.g., pregabalin) in treating painful peripheral neuropathies may be considered as strong support for the present assertion that (S,S) reboxetine would have a reasonable likelihood of success in treating painful peripheral neuropathy.

20. All statements made herein are of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under 18 USC § 1001 and may jeopardize the validity of the application or any patent which may issue thereon.

Declared at Sandwich in the county of Kent in England this 31st day of July 2006 2006 by

M. J. Stoker

Malcolm John Stoker

before me

Notary Public MY COMMISSION EXPIRES WITH LIFE.

Andrew Martin Johnson B.A.
NOTARY PUBLIC
22 St. George's Place
Canterbury
CT1 1UT, England
Tel: 01227 479479

Exhibit "A"

The Merck Manual of Diagnosis and Therapy, 16th ed., pp. 1518-23 (Merck Research Labs., Rahway, NJ, 1992)

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THORACIC OUTLET OBSTRUCTION SYNDROMES

(Neurovascular Compression Syndromes of the Shoulder Girdle; Scalenus Anticus Syndrome; Cervical Rib Syndrome)

A group of ill-defined syndromes characterized by symptoms of pain and paresthesias in the hand, neck, shoulder, or arms. They are most often distributed medially in the arms and sometimes extend into the adjacent anterior chest wall. The conditions are more common in women and most frequent between ages 35 and 55. Many patients have minor to moderate degrees of sensory impairment in the C-8 to T-1 distribution on the painful side, and a few will have prominent vascular-autonomic changes in the hand including cyanosis, swelling, and (rarely) Raynaud's phenomenon or distal gangrene. The pathogenesis is uncertain. Some authorities attribute the changes to compression of the subclavian vessels and, sometimes, the lower or medial trunks of the brachial plexus against a cervical rib, an abnormal 1st thoracic rib, or a putatively abnormal insertion or position of the scalene muscles.

Symptoms, Signs, and Diagnosis

More accurate imaging methods and the development of specific tests for nerve and root function have removed from this category the most frequent offenders; ie, carpal tunnel compression of the median nerve and spondylitic nerve root compression. The true neurovascular condition can be suspected by the distribution of symptoms. Diagnosis is supported by the finding of obliteration of the radial pulse when the patient fully inspires and then holds the breath and simultaneously hyperextends the neck and turns the head toward the unaffected side **(Adson's test)**, or when the arm is elevated to 90° and rotated externally with the elbow at a right angle and the head is turned forcibly to the unaffected side **(Allen test)**. Also helpful is the auscultation of bruits at the clavicle or the apex of the axilla, or the finding of a cervical rib by x-ray. Some patients will show kinking or partial obstruction of axillary arteries or veins on angiography, but these are not incontrovertible evidence of disease.

Treatment

Most patients respond to physical therapy and exercises. Except when obvious cervical ribs or subclavian artery obstructions can be identified, operation is best avoided or the decision left to the experienced specialist.

PERIPHERAL NEUROPATHY

A syndrome of sensory loss, muscle weakness and atrophy, decreased deep tendon reflexes, and vasomotor symptoms, singly or in any combination. These may occur with disease of a single nerve ***(mononeuropathy)****, 2 or more nerves in separate areas* ***(multiple mononeuropathy)****, or many nerves simultaneously* ***(polyneuropathy)****.* Either the axon (diabetes, uremia, toxic agents) or the myelin sheath/Schwann cell (acute and chronic inflammatory polyneuropathy, leukodystrophies) may be the primary site of injury. Small myelinated fibers, causing primary loss of temperature and pain sensation, or large fibers, causing motor or proprioceptive defects, may be affected. Some neuropathies (lead, dapsone, tick, porphyria, Guillain-Barré) primarily involve motor fibers, whereas others mainly affect the dorsal root ganglia or sensory fibers producing sensory symptoms (dorsal root ganglionitis of cancer, leprosy, AIDS, diabetes, and chronic pyridoxine intoxication). Occasionally, cranial nerves also are involved (Guillain-Barré, diabetes mellitus, diphtheria). Knowing the particular modalities involved helps the physician determine the cause, although some neuropathies remain undiagnosed. AIDS should always be considered in poorly explained cases occurring in epidemic areas.

Etiology

Trauma is the most common cause of a localized injury to a single nerve. **Pressure** paralysis usually affects superficial nerves (ulnar, radial, peroneal) at bony prominences (eg, during sound sleep or anesthesia in thin or cachectic persons and often in alcoholics) or at narrow canals (eg, in entrapment neuropathies, such as the median nerve in the carpal

tunnel syndrome). Pressure palsies also may result from tumors, bony hyperostosis, casts, crutches, or prolonged cramped postures (eg, from gardening). **Violent muscular activity or forcible overextension of a joint** may produce a focal neuropathy, as may repeated small traumas (eg, those encountered by engravers through tight gripping of small tools, or by air-hammer operators through excessive vibration). **Hemorrhage** into a nerve and **exposure to cold or radiation** may cause neuropathy.

Multiple mononeuropathy usually is secondary to collagen-vascular disorders (polyarteritis nodosa, SLE, scleroderma, sarcoidosis, and RA), metabolic diseases (diabetes mellitus), or infectious diseases (Lyme disease, HIV).

Microorganisms may cause mononeuropathy by direct invasion of the nerve (eg, leprosy). Polyneuropathy with acute febrile diseases may be due to a toxin (diphtheria), or an autoimmune reaction (Guillain-Barré syndrome); the polyneuropathy that sometimes follows immunizations also is probably autoimmune (see also Ch. 127 and ACUTE VIRAL ENCEPHALITIS in Ch. 125).

Toxic agents generally cause a polyneuropathy, but sometimes a mononeuropathy. They include emetine, hexobarbital, barbital, chlorobutanol, sulfonamides, phenytoin, nitrofurantoin, the vinca alkaloids, heavy metals, CO, triorthocresylphosphate, orthodinitrophenol, many solvents, and other industrial poisons.

Nutritional deficiency and metabolic disorders may result in polyneuropathy. Deficiency of B vitamins is often the cause (eg, in alcoholism, beriberi, pernicious anemia, isoniazid-induced pyridoxine deficiency, malabsorption syndromes, and hyperemesis gravidarum). Polyneuropathy also occurs in hypothyroidism, porphyria, sarcoidosis, amyloidosis, and uremia. Diabetes mellitus causes several forms of neuropathy: sensorimotor distal polyneuropathy (most common), multiple mononeuropathy, and focal mononeuropathy (eg, of oculomotor or abducens cranial nerves).

Malignancy may cause a polyneuropathy secondary to a monoclonal gammopathy (multiple myeloma, lymphoma) or amyloid invasion of the nerves themselves, and/or nutritional deficiencies.

Symptoms, Signs, and Clinical Forms

Mononeuropathy, both single and multiple, is characterized by pain, weakness, and paresthesias in the distribution of the affected nerve. Multiple mononeuropathy is asymmetric, and all the affected nerves may be involved from the outset or progressively. Extensive involvement of many nerves may simulate a polyneuropathy.

Compression and entrapment neuropathies result from mechanical compromise of a nerve. **Ulnar nerve palsy** is often caused by trauma to the nerve in the ulnar groove of the elbow by repeated leaning on the elbow or by asymmetric bone growth after a childhood fracture ("tardy ulnar palsy"). Ulnar nerve compression can also occur at the cubital tunnel. There are paresthesias and sensory deficit in the 5th and lateral half of the 4th fingers, plus weakness and atrophy of the thumb adductor, 5th finger abductor, and interossei muscles. Severe, chronic ulnar palsy produces a "claw-hand" deformity. Accurate nerve conduction studies identify the site of the lesion. Conservative treatment should be attempted, as surgical repair is often unsuccessful. The **carpal tunnel syndrome** results from compression of the median nerve in the volar aspect of the wrist between the longitudinal tendons of forearm muscles that flex the hand and the transverse superficial carpal ligament. This compression produces paresthesias in the radial-palmar aspect of the hand plus pain in the wrist, in the palm, or sometimes proximal to the compression site in the forearm and shoulder. The pain may be more severe at night. Sensory deficit in the palmar aspect of the first 3 digits and/or weakness and atrophy in muscles controlling thumb abduction and apposition may follow. The syndrome is relatively common, may be uni- or bilateral, and occurs more often in women. It is particularly associated with occupations that require repeated forceful wrist flexion and also with acromegaly, myxedema, and fluid changes of pregnancy. The chief distinction to be made is from C-6 root compression due to cervical

radiculopathy. **Treatment:** Performing tasks requiring forceful wrist flexion should be discontinued. Cock-up splints help to relieve night pain and take pressure off the nerve for a limited time. Local corticosteroid injections occasionally bring temporary relief. If symptoms continue or progress, surgical decompression of the median nerve at the wrist is required.

Peroneal nerve palsy is usually caused by compression of the nerve against the lateral aspect of the fibular neck. It is most common in emaciated bedridden patients and in thin people who habitually cross their legs. Weakness of foot dorsiflexion and eversion (foot drop) are present. Occasionally, a sensory deficit is found over the anterolateral aspect of the lower leg and dorsum of the foot or in the web space between the 1st and 2nd metatarsals. **Radial nerve palsy** ("Saturday night palsy") is caused by compression of the nerve against the humerus—eg, as the arm is draped over the back of a chair during intoxication or deep sleep. Symptoms include weakness of wrist and finger extensors (wrist drop) and occasionally sensory loss over the dorsal aspect of the 1st dorsal interosseous muscle.

The site of local nerve damage may be identified by **Tinel's sign,** *a distal paresthesia in the distribution of the nerve that is elicited by percussion over the site of compression.* Nerve conduction studies and electromyography are most helpful in localization.

Polyneuropathy is relatively symmetric; sensory, motor, and vasomotor fibers often are involved simultaneously. (An acute, rapidly progressive form, the Guillain-Barré syndrome, and hereditary neuropathies are discussed separately below.) The most common form of polyneuropathy, seen with metabolic diseases (eg, diabetes mellitus, renal failure, malnutrition), develops slowly, often over months or years; it frequently begins with sensory abnormalities in the lower extremities. Abnormalities are often more severe distally than proximally. Peripheral tingling, numbness, burning pain, or deficiencies in joint proprioception and vibratory sensation often are prominent. Pain is often worse at night and may be aggravated by touching the affected area or by temperature changes. In severe cases, objective signs of sensory loss, typically with stocking-and-glove distribution, can be shown. The Achilles and other deep tendon reflexes are diminished or absent. Painless ulcers on the digits or Charcot's joints may be seen when sensory loss is profound. Sensory or proprioceptive deficits may lead to gait abnormalities. Motor involvement results in distal muscle weakness and atrophy.

The autonomic nervous system may be additionally or selectively involved, leading to nocturnal diarrhea, bladder and bowel incontinence, impotence, or postural hypotension. Vasomotor symptoms are variable. The skin may be paler and drier than normal or there may be excess sweating and/or dusky discoloration. Trophic changes are common in severe and prolonged cases; they consist of smooth, shiny skin, pitted or ridged nails, and osteoporosis.

Uncommonly, an exclusively sensory polyneuropathy is seen, which begins with peripheral pains and paresthesias and progresses centrally to a loss of all forms of sensation. This occurs as a remote effect of carcinoma, especially bronchogenic, after megadose intoxication with pyridoxine (B_6), in amyloidosis, hypothyroidism, myeloma, and uremia.

Diagnosis

Neuropathy is a symptom complex rather than a disease entity, and the cause must be sought. Clues to a systemic disorder may be found on physical examination or from the history. These include rash, skin ulcers, Raynaud's phenomenon, weight loss, fever, lymphadenopathy, or mass lesions.

Laboratory findings often are helpful. A CBC may show the megaloblasts of pernicious anemia, or the stippled RBCs of lead poisoning. Abnormal liver function tests and alkaline phosphatase may suggest an underlying malignancy. Blood creatinine and glucose may suggest a diagnosis of renal failure or diabetes mellitus. Urine should be checked for porphyrinogens, porphobilinogens, and heavy metals. Abnormal serum protein and immunoelectrophoresis may support a diagnosis of neuropathy associated with multiple myeloma or monoclonal gammopathy. Cryoglobulins or complement fixations should be

checked in appropriate settings. Thyroid function should be evaluated, including thyroid-stimulating hormone, in patients with carpal tunnel syndrome.

Electromyography (EMG) and **nerve conduction velocity tests** help confirm neuropathy, and document specific nerve involvement and the predominant type of fiber involved (sensory, motor). Demyelinating lesions slow nerve conductions, and focal demyelinating blocks may be documented. An axonal process causes spontaneous activity on EMG along with low amplitude evoked responses, and relatively preserved conduction velocities on nerve conduction studies. In carpal tunnel syndrome, conduction slows across the carpal ligament, prolonging the latency to the abductor pollicis brevis or blocking it altogether. The distal sensory latency is similarly lengthened. Ulnar motor and sensory distal latencies must be normal in the same arm. **Muscle biopsy** may sometimes provide specific diagnoses (trichinosis, sarcoidosis, polyarteritis). Sural nerve biopsies rarely are indicated.

Prognosis and Treatment

Treatment of the systemic disorder (diabetes, renal failure, multiple myeloma, or tumor) may halt progression and improve symptoms, but recovery is slow. Traumatic lesions with complete transection of the nerve require surgical apposition. Entrapment neuropathies may require corticosteroid injections or surgical decompression. Physical therapy and splints reduce the likelihood or severity of contractures.

GUILLAIN–BARRÉ SYNDROME (GBS)

(Acute Polyneuropathy; Acute Polyradiculitis; Infectious or Acute Idiopathic Polyneuropathy; Landry's Ascending Paralysis; Acute Segmentally Demyelinating Polyradiculoneuropathy)

An acute, usually rapidly progressive form of inflammatory polyneuropathy characterized by muscular weakness and mild distal sensory loss that about ⅔ of the time begins 5 days to 3 wk after a banal infectious disorder, surgery, or an immunization. GBS is the most frequently acquired demyelinating neuropathy. The **cause** is unknown, although an autoimmune basis is probable. Histologically, focal areas of segmental demyelination with perivascular and endoneurial infiltration of lymphocytes and monocytes are scattered along the peripheral nerves, roots, and cranial nerves. In severe lesions, axonal degeneration accompanies the segmental demyelination.

Symptoms and Signs

Relatively symmetric weakness accompanied by paresthesias usually begins in the legs and progresses to the arms. Weakness always is more prominent than sensory symptoms or signs, and may be most prominent proximally. Deep tendon reflexes are lost. Sphincters usually are spared. More than 50% of severely involved patients have weakness of facial and oropharyngeal muscles, and 5 to 10% require intubation for respiratory failure. Autonomic dysfunction, including BP fluctuations, inappropriate ADH secretion, cardiac arrhythmias, and pupillary changes occur in more severely involved patients. The respiratory paralysis and the autonomic defects may be life-threatening. Despite advances in respiratory care, up to 5% of patients die; 90% of patients reach their maximal degree of weakness in 3 wk, most in the first 2 wk.

In an unusual variant of acute idiopathic polyneuropathy, patients may develop only ophthalmoparesis, ataxia, and areflexia. It is important in such cases to rule out myasthenia gravis, acute thiamine deficiency, and, rarely, botulism.

Diagnosis

Diagnosis of acute GBS is based on the clinical syndrome. Laboratory studies include increased protein without increased cells in the CSF. Electrophysiologic abnormalities support the diagnosis, but the latter are hardly necessary in typical cases. Two-thirds of patients will have slow nerve conduction velocities and evidence of segmental demyelination at the time of onset. F-wave latencies, evidence of proximal demyelination, tend to be

prolonged. Antecedent mononucleosis, or cytomegalovirus infections, mumps, or rubella can be excluded by appropriate serologic tests but do not change the prognosis.

Differential diagnosis includes toxins that act at the neuromuscular junction (eg, organic phosphates, and botulism—see OTHER DISORDERS OF NEUROMUSCULAR TRANSMISSION, below, and Ch. 55). Acute poliomyelitis occurs in epidemics and produces fever, malaise, and pleocytosis in the CSF. Serologic studies are available. Tick infestation of the scalp causes an acute ascending motor neuropathy, mainly in children. Deep tendon reflexes are lost; sensation is normal. Removal of the tick results in resolution of all symptoms.

Prognosis and Treatment

Severe acute polyneuropathy is a medical emergency, requiring constant monitoring and vigorous support of vital functions. The airway must be kept clear, and vital capacity should be measured frequently, so that respiration can be assisted if necessary. Fluid intake should be sufficient to maintain a urine volume of at least 1 to 1.5 L/day; serum electrolytes should be monitored to prevent water intoxication. The extremities should be protected from trauma and from pressure of bedclothes. Heat helps relieve pain and permits early physical therapy. Immobilization may cause ankylosis and is to be avoided. Passive full-range joint movement should be started immediately and active exercises begun when acute symptoms subside. Heparin 5000 u. s.c. bid may be beneficial while the patient is bedridden.

Corticosteroids worsen the outcome in GBS and should *not* be used. **Plasmapheresis** (see also in Ch. 94) has been shown to be beneficial when carried out early in the disease and is the treatment of choice in patients acutely ill with GBS. It is a relatively safe procedure that shortens the disease course, lowers mortality, lessens the incidence of permanent paralysis, and abbreviates hospitalization.

Considerable improvement over a period of months is usual; about 30% of adults have residual weakness at 3 yr and the percentage is higher in children. Residual defects may require retraining, orthopedic appliances, or operation. About 10% of patients relapse after initial improvement and enter a chronic state **(chronic relapsing polyneuropathy)**. Pathology and laboratory data are similar to acute cases, but the weakness may be more asymmetric and progress more slowly. Nerves eventually become palpable from repeated episodes of segmental demyelination and remyelination. Corticosteroids improve weakness in the chronic state, and prolonged therapy may be necessary. Immunosuppressive agents (azathioprine) and plasmapheresis benefit some patients.

HEREDITARY NEUROPATHIES

Hereditary neuropathies are classified as either hereditary sensory-motor neuropathies **(HSMN)** or hereditary sensory neuropathies **(HSN)**. (The hereditary motor neuropathies are discussed under motor neuron diseases. Neurofibromatosis, a distinct hereditary neuropathy with prominent skin involvement, and Charcot-Marie-Tooth disease, the most common HSMN, previously known as peroneal muscular atrophy, are described separately, below.) Other less common HSMN begin from birth, and patients are more disabled. HSN are rare. Loss of distal pain and temperature modalities are more prominent than vibratory and position loss. The main problem in these patients is pedal mutilation due to insensitivity to pain with frequent infections and osteomyelitis. Good foot care is mandatory.

PERONEAL MUSCULAR ATROPHY; HYPERTROPHIC INTERSTITIAL NEUROPATHY

(Charcot-Marie-Tooth Disease; Dejerine-Sottas Disease)

Peroneal muscular atrophy (Charcot-Marie-Tooth [CMT] disease) is a relatively common hereditary (usually autosomal dominant) disorder of the peripheral nervous system characterized by weakness and atrophy, primarily in peroneal and distal leg muscles. Other degenerative diseases (eg, Friedreich's ataxia) may be present in these patients or in the same family pedigrees.

Symptoms and Signs

Type 1 patients present in middle childhood with foot drop and slowly progressive distal muscle atrophy producing "stork leg deformity." Intrinsic muscle wasting in the hand begins later. A stocking-glove decrease in vibration, pain, and temperature is present. Deep tendon reflexes are absent. Foot deformities, ie, high pedal arches or hammer toes, may be the only signs in less affected family members who carry the trait. Type 1 patients have slow nerve conduction velocities with prolonged distal latencies. Pathologic specimens show segmental demyelination and remyelination. Enlarged peripheral nerves may be palpated. The disease progresses slowly and is compatible with a normal life span. Patients with **type 2 CMT** disease usually develop weakness later in life, and the process is slower in evolution. They have relatively normal nerve conduction velocities but low amplitude evoked potentials, and biopsies reveal wallerian degeneration.

Hypertrophic interstitial neuropathy (Dejerine-Sottas disease), a rare autosomal recessive disorder of the peripheral nerves, presents in childhood with progressive weakness and sensory loss with absent deep tendon reflexes. It initially resembles CMT disease, but motor weakness progresses at a faster rate. This is also a demyelinating-remyelinating disorder with enlarged peripheral nerves and "onion bulbs" on biopsy.

Diagnosis and Treatment

The characteristic distribution of motor weakness, foot deformities, family history, and electrophysiologic abnormalities confirm the diagnosis. No specific treatment is available. Vocational counseling to anticipate disease progression may be useful in young patients. Bracing helps correct foot drop; orthopedic surgery to stabilize the foot may be of value.

NEUROFIBROMATOSIS

A pair of autosomal dominant disorders designated type 1 (sometimes called von Recklinghausen's disease) and carried on chromosome 17, and type 2 characterized by bilateral acoustic neuromas (see TABLE 131–2).

Symptoms, Signs, and Diagnosis

One third of patients with neurofibromatosis type 1 are asymptomatic and discovered on routine examination. In ⅓ of patients cosmetic problems are the initial complaints. Characteristic skin lesions, apparent at birth or in infancy in > 90% of patients, are medium-brown (café au lait) macules distributed most commonly over the trunk, pelvis, and flexor creases of elbows and knees. The presence of 6 or more of these freckle-like lesions with one > 1.5 cm is diagnostic of neurofibromatosis. Multiple cutaneous tumors, flesh-colored and of variable size and shape, appear in late childhood. There may be only a few or thousands of these lesions. Subcutaneous nodules or amorphous overgrowth of subcutaneous tissues **(plexiform neuromas)** and underlying bone may produce grotesque deformities (which are rare). Skeletal anomalies include absence of the greater wing of the sphenoid bone (posterior orbital wall) with consequent pulsating exophthalmos, fibrous dysplasia, subperiosteal bone cysts, vertebral scalloping, scoliosis, and pseudarthrosis.

The remaining ⅓ of patients present with neurologic problems. **Neurofibromas** (tumors of Schwann cells and nerve fibroblasts), which rarely appear before puberty, can be felt along the course of subcutaneous peripheral nerves. These tumors may involve spinal nerve roots, characteristically growing through an intervertebral foramen to produce intraspinal and extraspinal masses ("dumbbell" tumor). The intraspinal component may cause spinal cord compression. Plexiform neuromas may involve peripheral nerves producing deficits distal to the lesion. Tumors of cranial nerves may produce progressive blindness (optic glioma) or dizziness, ataxia, and deafness (acoustic neuroma). A study of neurofibromatosis showed a 40 (male) to 87 (female) times increase in risk for neural tumors vs. the general population. The type 1 neurofibromatosis tumors, ranging in number from one or two to hundreds, occur in 5 to 10%. Recurrence is common and, in most cases, the disease is progressive.

Exhibit "B"

European Summary of Product Characteristics (SPC) for the LYRICA® product, available at http://emc.medicines.org.uk/emc/assets/c/html/displaydoc.asp?DocumentID=1461 (Accessed: July 21, 2006) (16 pages).

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Lyrica Capsules ■

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1. NAME OF THE MEDICINAL PRODUCT

LYRICA▼ 25 mg hard capsules

LYRICA▼ 50 mg hard capsules

LYRICA▼ 75 mg hard capsules

LYRICA▼ 100 mg hard capsules

LYRICA▼ 150 mg hard capsules

LYRICA▼ 200 mg hard capsules

LYRICA▼ 225 mg hard capsules

LYRICA▼ 300 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg or 300 mg of pregabalin. Lyrica capsules also contain lactose. For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule

25 mg capsule: White hard gelatine capsule, marked "Pfizer" on the cap and "PGN 25" on the body with black ink.

50 mg capsule: White hard gelatine capsule, marked "Pfizer" on the cap and "PGN 50" on the body with black ink. The body is also marked with a black band.

75 mg capsule: White and orange hard gelatine capsule, marked "Pfizer" on the cap and "PGN 75" on the body with black ink.

100 mg capsule: Orange hard gelatine capsules, marked "Pfizer" on the cap and "PGN 100" on the body with black ink.

150 mg capsule: White hard gelatine capsule, marked "Pfizer" on the cap and "PGN 150" on the body with black ink.

200 mg capsule: Light orange hard gelatine capsules, marked "Pfizer" on the cap and "PGN 200" on the body with black ink.

225 mg capsule: White and orange hard capsule, marked "Pfizer" on the cap and "PGN 225" on the body with black ink.

300 mg capsule: White and orange hard gelatine capsule, marked "Pfizer" on the cap and "PGN 300" on the body with black ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Neuropathic pain

Lyrica is indicated for the treatment of peripheral neuropathic pain in adults.

Epilepsy

Lyrica is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalisation.

Generalised Anxiety Disorder

LYRICA is indicated for the treatment of Generalised Anxiety Disorder (GAD) in adults.

4.2 Posology and method of administration

The dose range is 150 to 600 mg per day given in either two or three divided doses.

Lyrica may be taken with or without food.

Neuropathic pain

Pregabalin treatment can be started at a dose of 150 mg per day. Based on individual patient response and tolerability, the dosage may be increased to 300 mg per day after an interval of 3 to 7 days, and if needed, to a maximum dose of 600 mg per day after an additional 7-day interval.

Epilepsy

Pregabalin treatment can be started with a dose of 150 mg per day. Based on individual patient response and tolerability, the dosage may be increased to 300 mg per day after 1 week. The maximum dosage of 600 mg per day may be achieved after an additional week.

Generalised Anxiety Disorder

The dose range is 150 to 600 mg per day given as two or three divided doses. The need for treatment should be reassessed regularly.

Pregabalin treatment can be started with a dose of 150 mg per day. Based on individual patient response and tolerability, the dosage may be increased to 300 mg per day after 1 week. Following an additional week the dosage may be increased to 450 mg per day. The maximum dosage of 600 mg per day may be achieved after an additional week.

Discontinuation of pregabalin

In accordance with current clinical practice, if pregabalin has to be discontinued it is recommended this should be done gradually over a minimum of 1 week independent of the indication (see section 4.8).

Patients with renal impairment

Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug. As pregabalin clearance is directly proportional to creatinine clearance (see section 5.2), dosage reduction in patients with compromised renal function must be individualised according to creatinine clearance (CL_{cr}), as indicated in Table 1 determined using the following formula:

$$CL_{cr}(ml/min) = \left[\frac{1.23 \times [140 - age(years)] \times weight(kg)}{serum\ creatinine\ (\mu mol/l)}\right] (\times 0.85\ for\ female\ patients)$$

Pregabalin is removed effectively from plasma by haemodialysis (50% of drug in 4 hours). For patients receiving haemodialysis, the pregabalin daily dose should be adjusted based on renal function. In addition to the daily dose, a supplementary dose should be given immediately following every 4-hour haemodialysis treatment (see Table 1).

Table 1. Pregabalin dosage adjustment based on renal function

Creatinine Clearance (CL_{cr}) (ml/min)	Total Pregabalin Daily dose *		Dose Regimen
	Starting dose (mg/day)	Maximum dose (mg/day)	
≥ 60	150	600	BID or TID
≥ 30 - <60	75	300	BID or TID
≥ 15 - <30	25 – 50	150	Once Daily or BID
< 15	25	75	Once Daily
Supplementary dosage following haemodialysis (mg)			
	25	100	Single dose+

TID = Three divided doses

BID = Two divided doses

* Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose

+ Supplementary dose is a single additional dose

Use in patients with hepaticimpairment

No dosage adjustment is required for patients with hepatic impairment (see section 5.2).

Use in children and adolescents

Lyrica is not recommended for use in children below the age of 12 years and adolescents (12 - 17 years of age) due to insufficient data on safety and efficacy (see section 5.3).

Use in the elderly (over 65 years of age)

Elderly patients may require a dose reduction of pregabalin due to a decreased renal function (see patients with renal impairment).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

In accordance with current clinical practice, some diabetic patients who gain weight on pregabalin treatment may need to adjust hypoglycaemic medications.

Pregabalin treatment has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall) in the elderly population. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medication.

There are insufficient data for the withdrawal of concomitant antiepileptic medicinal products, once seizure control with pregabalin in the add-on situation has been reached, in order to reach monotherapy on pregabalin.

After discontinuation of short-term and long-term treatment with pregabalin withdrawal symptoms have been observed in some patients. The following events have been mentioned: insomnia, headache, nausea, diarrhoea, flu syndrome, nervousness, depression, pain, sweating and dizziness. The patient should be informed about this at the start of the treatment.

Concerning discontinuation of long-term treatment of pregabalin there are no data of the incidence and severity of withdrawal symptoms in relation to duration of use and dosage of pregabalin.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Since pregabalin is predominantly excreted unchanged in the urine, undergoes negligible metabolism in humans (<2% of a dose recovered in urine as metabolites), does not inhibit drug metabolism *in vitro*, and is not bound to plasma proteins, it is unlikely to produce, or be subject to, pharmacokinetic interactions.

Accordingly, in *in vivo* studies no clinically relevant pharmacokinetic interactions were observed between pregabalin and phenytoin, carbamazepine, valproic acid, lamotrigine, gabapentin, lorazepam, oxycodone or ethanol. Population pharmacokinetic analysis indicated that oral antidiabetics, diuretics, insulin, phenobarbital, tiagabine and topiramate had no clinically significant effect on pregabalin clearance.

Co-administration of pregabalin with the oral contraceptives norethisterone and/or ethinyl oestradiol does not influence the steady-state pharmacokinetics of either substance.

Multiple oral doses of pregabalin co-administered with oxycodone, lorazepam, or ethanol did not result in clinically important effects on respiration. Pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone. Pregabalin may potentiate the effects of ethanol and lorazepam.

No specific pharmacodynamic interaction studies were conducted in elderly volunteers. Interaction studies have only been performed in adults.

4.6 Pregnancy and lactation

There are no adequate data on the use of pregabalin in pregnant women.

Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk to humans is unknown. Lyrica should not be used during pregnancy unless clearly necessary (if the benefit to the mother clearly outweighs the potential risk to the foetus). . Effective contraception must be used in women of child bearing potential.

It is not known if pregabalin is excreted in the breast milk of humans; however, it is present in the milk of rats. Therefore, breast-feeding is not recommended during treatment with pregabalin.

4.7 Effects on ability to drive and use machines

Lyrica may have minor or moderate influence on the ability to drive and use machines. Lyrica may cause dizziness and somnolence and therefore may influence the ability to drive or use machines. Patients are advised not to drive, operate complex machinery or engage in other potentially hazardous activities until it is known whether this medication affects their ability to perform these activities.

4.8 Undesirable effects

The pregabalin clinical programme involved over 9000 patients who were exposed to pregabalin, of whom over 5000 were in double-blind placebo controlled trials. The most commonly reported adverse reactions were dizziness and somnolence. Adverse reactions were usually mild to moderate in intensity. In all controlled studies, the discontinuation rate due to adverse reactions was 13% for patients receiving pregabalin and 7% for patients receiving placebo. The most common adverse reactions resulting in discontinuation from pregabalin treatment groups were dizziness and somnolence.

In the table below all adverse reactions, which occurred at an incidence

greater than placebo and in more than one patient, are listed by class and frequency (very common (> 1/10), common (> 1/100, < 1/10), uncommon (>1/1000, <1/100) and rare (<1/1000)).

The adverse reactions listed may also be associated with the underlying disease and / or concomitant medications.

Body System	Adverse drug reactions
Blood and lymphatic system disorders	
Rare	Neutropenia
Metabolism and nutrition disorders	
Common	Appetite increased
Uncommon	Anorexia
Rare	Hypoglycaemia
Psychiatric disorders	
Common	Euphoric mood, confusion, irritability, libido decreased
Uncommon	Hallucination, panic attack, restlessness, agitation, depression, depressed mood, mood swings, depersonalisation, insomnia exacerbated, word finding difficulty, abnormal dreams, libido increased, anorgasmia, apathy
Rare	Disinhibition, elevated mood
Nervous system disorders	
Very Common	Dizziness, somnolence
Common	Ataxia, coordination abnormal, tremor, dysarthria, memory impairment, disturbance in attention, paraesthesia
Uncommon	Syncope, stupor, myoclonus, psychomotor hyperactivity, visual field defect, ageusia, dyskinesia, dizziness postural, intention tremor, nystagmus, cognitive disorder, speech disorder, hyporeflexia, hypoaesthesia, amnesia, hyperaesthesia, burning sensation
Rare	Hypokinesia, parosmia, dysgraphia
Eye disorders	
Common	Vision blurred, diplopia
Uncommon	Visual disturbance, eye swelling, visual acuity reduced, eye pain, asthenopia, dry eye,

	lacrimation increased
Rare	Peripheral vision loss, oscillopsia, altered visual depth perception, photopsia, eye irritation, mydriasis, strabismus, visual brightness
Ear and labyrinth disorders	
Common	Vertigo
Rare	Hyperacusis
Cardiac disorders	
Uncommon	Tachycardia
Rare	Atrioventricular block first degree, sinus tachycardia, sinus arrhythmia, sinus bradycardia
Vascular disorders	
Uncommon	Flushing, hot flushes
Rare	Hypotension, hypertension, peripheral coldness,
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea, nasal dryness
Rare	Epistaxis, throat tightness, nasopharyngitis, cough, nasal congestion, rhinitis, snoring
Gastrointestinal disorders	
Common	Dry mouth, constipation, vomiting, flatulence
Uncommon	Abdominal distension, gastrooesophageal reflux disease, salivary hypersecretion, hypoaesthesia oral
Rare	Ascites, pancreatitis, dysphagia
Skin and subcutaneous tissue disorders	
Uncommon	Rash papular, sweating
Rare	Urticaria, cold sweat
Musculoskeletal and connective tissue disorders	
Uncommon	Muscle twitching, joint swelling, muscle cramp, myalgia, arthralgia, back pain, pain in limb, muscle stiffness
Rare	Rhabdomyolysis, cervical spasm, neck pain
Renal and urinary disorders	

Uncommon	Urinary incontinence, dysuria
Rare	Renal failure, oliguria
Reproductive system and breast disorders	
Common	Erectile dysfunction
Uncommon	Ejaculation delayed, sexual dysfunction
Rare	Amenorrhoea, breast discharge, breast pain, dysmenorrhoea, hypertrophy breast
General disorders and administration site conditions	
Common	Gait abnormal, feeling drunk, fatigue, oedema peripheral, oedema,
Uncommon	Fall, chest tightness, asthenia, thirst
Rare	Anasarca, face oedema, swollen tongue, pyrexia, rigors, pain exacerbated,
Investigations	
Common	Weight increased
Uncommon	Blood creatine phosphokinase increased, alanine aminotransferase increased, aspartate aminotransferase increased, platelet count decreased
Rare	Blood glucose increased, blood potassium decreased, white blood cell count decreased, blood creatinine increased, weight decreased

After discontinuation of short-term and long-term treatment with pregabalin withdrawal symptoms have been observed in some patients. The following events have been mentioned: insomnia, headache, nausea, diarrhoea, flu syndrome, nervousness, depression, pain, sweating and dizziness. The patient should be informed about this at the start of the treatment.

Concerning discontinuation of long-term treatment of pregabalin there are no data of the incidence and severity of withdrawal symptoms in relation to duration of use and dosage of pregabalin.

4.9 Overdose

In overdoses up to 15 g, no unexpected adverse reactions were reported. Treatment of pregabalin overdose should include general supportive measures and may include haemodialysis if necessary (see section 4.2 Table 1).

5. PHARMACOLOGICAL PROPERTIES

5.1

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics, ATC code: N03AX16

The active substance, pregabalin, is a gamma-aminobutyric acid analogue ((S)-3-(aminomethyl)-5-methylhexanoic acid).

Mechanism of action

Pregabalin binds to an auxiliary subunit (α_2-δ protein) of voltage-gated calcium channels in the central nervous system, potently displacing [^{3}H]-gabapentin.

Clinical experience

Neuropathic pain

Efficacy has been shown in studies in diabetic neuropathy and post herpetic neuralgia. Efficacy has not been studied in other models of neuropathic pain.

Pregabalin has been studied in 9 controlled clinical studies of up to 13 weeks with twice a day dosing (BID) and up to 8 weeks with three times a day (TID) dosing. Overall, the safety and efficacy profiles for BID and TID dosing regimens were similar.

In clinical trials up to 13 weeks, a reduction in pain was seen by week 1 and was maintained throughout the treatment period.

In controlled clinical trials 35% of the pregabalin treated patients and 18% of the patients on placebo had a 50% improvement in pain score. For patients not experiencing somnolence, such an improvement was observed in 33% of patients treated with pregabalin and 18% of patients on placebo. For patients who experienced somnolence the responder rates were 48% on pregabalin and 16% on placebo.

Epilepsy

Pregabalin has been studied in 3 controlled clinical studies of 12 week duration with either twice a day dosing (BID) or three times a day (TID) dosing. Overall, the safety and efficacy profiles for BID and TID dosing regimens were similar.

A reduction in seizure frequency was observed by Week 1.

Generalised Anxiety Disorder

Pregabalin has been studied in 6 controlled studies of 4-6 week duration, an elderly study of 8 week duration and a long-term relapse prevention study with a double blind relapse prevention phase of 6 months duration.

Relief of the symptoms of GAD as reflected by the Hamilton Anxiety Rating Scale (HAM-A) was observed by Week 1.

In controlled clinical trials (4-8 week duration) 52% of the pregabalin treated patients and 38% of the patients on placebo had at least a 50% improvement in HAM-A total score from baseline to endpoint.

5.2 Pharmacokinetic properties

Pregabalin steady-state pharmacokinetics are similar in healthy volunteers, patients with epilepsy receiving anti-epileptic drugs and patients with chronic pain.

Absorption:

Pregabalin is rapidly absorbed when administered in the fasted state, with peak plasma concentrations occurring within 1 hourfollowing both single and multiple dose administration. Pregabalin oral bioavailability is estimated to be ≥ 90% and is independent of dose. Following repeated administration, steady state is achieved within 24 to 48 hours. The rate of pregabalin absorption is decreased when given with food resulting in a decrease in C_{max} by approximately 25-30% and a delay in t_{max} to approximately 2.5 hours. However, administration of pregabalin with food has no clinically significant effect on the extent of pregabalin absorption.

Distribution:

In preclinical studies, pregabalin has been shown to cross the blood brain barrier in mice, rats, and monkeys. Pregabalin has been shown to cross the placenta in rats and is present in the milk of lactating rats. In humans, the apparent volume of distribution of pregabalin following oral administration is approximately 0.56 l/kg. Pregabalin is not bound to plasma proteins.

Metabolism:

Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabelled pregabalin, approximately 98% of the radioactivity recovered in the urine was unchanged pregabalin. The N-methylated derivative of pregabalin, the major metabolite of pregabalin found in urine, accounted for 0.9% of the dose. In preclinical studies, there was no indication of racemisation of pregabalin S-enantiomer to the R-enantiomer.

Elimination:

Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug.

Pregabalin mean elimination half-life is 6.3 hours. Pregabalin plasma clearance and renal clearance are directly proportional to creatinine clearance (see section 5.2 Renal impairment).

Dosage adjustment in patients with reduced renal function or undergoing haemodialysis is necessary (see Section 4.2 Table 1).

Linearity / non-linearity :

Pregabalin pharmacokinetics are linear over the recommended daily dose range. Inter-subject pharmacokinetic variability for pregabalin is low (<20%). Multiple dose pharmacokinetics are predictable from single-dose data. Therefore, there is no need for routine monitoring of plasma concentrations of pregabalin.

Pharmacokinetics in special patient groups

Gender

Clinical trials indicate that gender does not have a clinically significant influence on the plasma concentrations of pregabalin.

Renal impairment

Pregabalin clearance is directly proportional to creatinine clearance. In addition, pregabalin is effectively removed from plasma by haemodialysis (following a 4 hour haemodialysis treatment plasma pregabalin concentrations are reduced by approximately 50%). Because renal elimination is the major elimination pathway, dosage reduction in patients with renal impairment and dosage supplementation following haemodialysis is necessary (see section 4.2 Table 1).

Hepatic impairment

No specific pharmacokinetic studies were carried out in patients with impaired liver function. Since pregabalin does not undergo significant metabolism and is excreted predominantly as unchanged drug in the urine, impaired liver function would not be expected to significantly alter pregabalin plasma concentrations.

Elderly (over 65 years of age)

Pregabalin clearance tends to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with decreases in creatinine

clearance associated with increasing age. Reduction of pregabalin dose may be required in patients who have age related compromised renal function (see section 4.2 Table 1).

5.3 Preclinical safety data

In conventional safety pharmacology studies in animals, pregabalin was well-tolerated at clinically relevant doses. In repeated dose toxicity studies in rats and monkeys CNS effects were observed, including hypoactivity, hyperactivity and ataxia. An increased incidence of retinal atrophy commonly observed in aged albino rats was seen after long term exposure to pregabalin at exposures ≥ 5 times the mean human exposure at the maximum recommended clinical dose.

Pregabalin was not teratogenic in mice, rats or rabbits. Foetal toxicity in rats and rabbits occurred only at exposures sufficiently above human exposure. In prenatal/postnatal toxicity studies, pregabalin induced offspring developmental toxicity in rats at exposures>2 times the maximum recommended human exposure.

Pregabalin is not genotoxic based on results of a battery of *in vitro* and *in vivo* tests.

Two-year carcinogenicity studies with pregabalin were conducted in rats and mice. No tumours were observed in rats at exposures up to 24 times the mean human exposure at the maximum recommended clinical dose of 600 mg/day. In mice, no increased incidence of tumours was found at exposures similar to the mean human exposure, but an increased incidence of haemangiosarcoma was observed at higher exposures. The non-genotoxic mechanism of pregabalin-induced tumour formation in mice involves platelet changes and associated endothelial cell proliferation. These platelet changes were not present in rats or in humans based on short term and limited long term clinical data. There is no evidence to suggest an associated risk to humans.

In juvenile rats the types of toxicity do not differ qualitatively from those observed in adult rats. However, juvenile rats are more sensitive. At therapeutic exposures, there was evidence of CNS clinical signs of hyperactivity and bruxism and some changes in growth (transient body weight gain suppression). Effects on the oestrus cycle were observed at 5-fold the human therapeutic exposure. Neurobehavioural/cognitive effects were observed in juvenile rats 1-2 weeks after exposure>2 times (acoustic startle response) or>5 times (learning/memory) the human therapeutic exposure.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:

Lactose monohydrate

Maize starch

Talc

Capsule shell:

Gelatin

Titanium Dioxide (E171)

Sodium Laurilsulphate

Silica, colloidal anhydrous

Purified water

75 mg, 100 mg, 200 mg, 225 mg and 300 mg shells only:

Red Iron Oxide (E172)

Printing Ink :

Shellac

Black Iron Oxide (E172)

Propylene Glycol

Potassium Hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

PVC/Aluminium blisters containing 14, 21, 56, 84 or 112 (2 x 56) hard capsules.

100 x 1 hard capsules in PVC/Aluminium perforated unit dose blisters.

HDPE bottle containing 200 hard capsules.

Not all pack sizes may be marketed

6.6 Instructions for use, handling and disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited,

Ramsgate Road,

Sandwich,

Kent

CT13 9NJ

UK

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/279/001 - 035

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06th July 2004

10. DATE OF REVISION OF THE TEXT

16th May 2006

11. LEGAL CATEGORY

POM

http://emc.medicines.org.uk/emc/assets/c/html/displaydoc.asp?DocumentID=14651

Exhibit "C"

ClinicalTrials.gov, "Neuropathic Pain Assessment Comparing Pregabalin and Paroxetine in Management of MS-Induced Neuropathic Pain," available at http://www.clincialtrials.gov/ct/show/NCT00291148?order=4 (Accessed: July 24, 2006) (4 pages).

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

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Neuropathic Pain Assessment Comparing Pregabalin and Paroxetine in Management of MS-Induced Neuropathic Pain

This study is not yet open for patient recruitment.
Verified by University of Manitoba January 2006

Sponsored by: University of Manitoba
Information provided by: University of Manitoba
ClinicalTrials.gov Identifier: NCT00291148

Purpose

This is a comparative drug trial involving patients with clinically definite Multiple Sclerosis and documented neuropathic pain. Patients will be randomized to receive treatment with either paroxetine or pregabalin. After dose titration, participants will complete various pain scale assessments at several points during the study in order to determine the effectiveness of their assigned pain medication.

Condition	Intervention	Phase
Neuropathic Pain Multiple Sclerosis	Drug: paroxetine Drug: pregabalin	Phase III

MedlinePlus related topics: Multiple Sclerosis; Pain

Study Type: Interventional
Study Design: Treatment, Randomized, Open Label, Uncontrolled, Parallel Assignment, Safety/Efficacy Study

Official Title: A Comparative Single Center, Randomized Neuropathic Pain Assessment Study Involving Patients With Clinically Definite Multiple Sclerosis (MS) Receiving Treatment With Either Pregabalin or Paroxetine

Further study details as provided by University of Manitoba:

Primary Outcomes: Pain levels (as determined by weekly Visual Analogue Scale for pain)
Secondary Outcomes: Short-Form 36 health outcomes survey (SF-36); Short-form McGill Pain Questionnaire (SF MPQ); Patient-rated Global Impression of Change (PGIC)
Expected Total Enrollment: 75

Study start: March 2006; Expected completion: September 2007

Data entry closure: March 2007

General Objective:

To determine the effectiveness of drug treatment in the management of MS-induced neuropathic pain.

Specific Objectives:

- Comparatively assess the effectiveness and safety profile of pregabalin (Lyrica) and paroxetine (Paxil) in managing MS-induced neuropathic pain.
- Comparatively assess the effectiveness of pregabalin (Lyrica) and paroxetine (Paxil) in improving the quality-of-life associated with MS-induced neuropathic pain.

Study Design:

A comparative single center, randomized, open-label study involving patients with multiple sclerosis (MS) – induced neuropathic pain receiving treatment with either pregabalin (Lyrica®) or paroxetine (Paxil®).

The study will run for approximately one year, requiring individual participants' involvement for 8 weeks.

Participant Selection:

Individuals with clinically definite MS presenting with symptoms of neuropathic pain (as determined by clinician) that express interest in the study will be screened for eligibility.

Inclusion Criteria:

- Patients presenting with symptoms of neuropathic pain as determined by clinician, with a minimum VAS pain score of 40mm as determined by a baseline score (0mm = no pain, 100mm = worst pain).
- Male and female patients between the ages of 18 and 65 years old.
- Clinically definite multiple sclerosis as defined by clinical history review, neurological examination and positive MRI.
- EDSS scores of < 6.0.
- No known hypersensitivity to the study medications.
- Negative serum pregnancy test for all female patients of childbearing age; not currently breastfeeding.
- Not currently treated with pregabalin, gabapentin, paroxetine or another SSRI.
- No previous treatment failures with pregabalin or paroxetine.
- Baseline creatinine clearance (Clcr) of > 50mL/min.
- No significant hepatic insufficiency.
- If on other pain medications, must be on stable dose for at least 6 months and

other medications must not elicit significant drug-drug interactions with study medications.

Study Procedures:

After obtaining informed consent (Visit 1), participants undergo various assessments, including pain/quality-of-life analyses (SF-MPQ, SF-36, VAS), physical/neurological exam and a standard blood test. Based on above inclusion criteria, participants will be randomized to either Group A (paroxetine) or Group B (pregabalin). Participants will be provided with prescriptions for assigned study medications as well as dosing instructions. A pain diary consisting of a single VAS scale will be provided to the participants, which are to be completed daily upon waking and should be used to rate the individual's average pain over the last 24 hours. Dosages of study medications will be titrated slowly over 3 weeks to lower likelihood of adverse events. After the three week titration phase, participants will return to the clinic (Visit 2) for a follow-up. Pain/quality-of-life assessments (as at Visit 1) will be completed again at this visit. In addition, average pain scores will be determined from daily pain diaries. Adverse events will be discussed and individual tolerability will be assessed. At this point, it will be determined if the patient will be maintained at the target dosage or if the dosage will be lowered to accommodate patient tolerability. Participants will be maintained at determined maintenance dose for 5 weeks, after which they will return to the clinic (Visit 3) for a final follow-up assessment. Participants will complete final pain/quality-of-life assessments, as well as the "Patient-rated Global Impression of Change". Adverse events and average pain scores will be reviewed. At the conclusion of the 8-week treatment phase, participants will have the option of remaining on their current study medication or be tapered off.

Eligibility

Ages Eligible for Study: 18 Years - 65 Years, Genders Eligible for Study: Both

Criteria

Inclusion Criteria:

- • Patients presenting with symptoms of neuropathic pain as determined by clinician, with a minimum VAS pain score of 40mm as determined by a baseline score (0mm = no pain, 100mm = worst pain).

 - Male and female patients between the ages of 18 and 65 years old.
 - Clinically definite multiple sclerosis as defined by clinical history review, neurological examination and positive MRI.
 - EDSS scores of < 6.0.
 - No known hypersensitivity to the study medications.
 - Negative serum pregnancy test for all female patients of childbearing age; not currently breastfeeding.
 - Not currently treated with pregabalin, gabapentin, paroxetine or another

SSRI.
- No previous treatment failures with pregabalin or paroxetine.
- Baseline creatinine clearance (Clcr) of > 50mL/min.
- No significant hepatic insufficiency.
- If on other pain medications, must be on stable dose for at least 6 months and other medications must not elicit significant drug-drug interactions with study medications.

Exclusion Criteria:

-

Location and Contact Information

Please refer to this study by ClinicalTrials.gov identifier NCT00291148

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Multiple Sclerosis Clinic, Health Sciences Centre, Winnipeg, Manitoba, R3T 2N2, Canada
Micheal P Namaka, Phd (204) 474-8380 namakamp@cc.umanitoba.ca
Maria Melanson, MD, Principal Investigator
Micheal P Namaka, PhD, Principal Investigator
Dana A Turcotte, B.Sc Pharm, Sub-Investigator

Study chairs or principal investigators

Micheal P Namaka, PhD, Principal Investigator, University of Manitoba
Maria Melanson, MD, Study Director, University of Manitoba

More Information

Study ID Numbers: MS_B2005:168
Last Updated: February 10, 2006
Record first received: February 10, 2006
ClinicalTrials.gov Identifier: NCT00291148
Health Authority: Canada: Ethics Review Committee
ClinicalTrials.gov processed this record on 2006-07-24

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National Institutes of Health, Department of Health & Human Services
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Exhibit "D"

ClinicalTrials.gov, "P4 (Pregabalin for Peripheral Posttraumatic Pain)," available at http://www.clinicaltrials.gov/ct/show/NCT00292188?order=15 (Accessed: July 24, 2006) (3 pages).

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P4 (Pregabalin for Peripheral Posttraumatic Pain)

This study is currently recruiting patients.
Verified by Pfizer March 2006

Sponsors and Collaborators: Pfizer
Pfizer Global Phamaceuticals, New York, USA

Information provided by: Pfizer

ClinicalTrials.gov Identifier: NCT00292188

Purpose

To evaluate the efficacy of pregabalin compared to placebo in the treatment of posttraumatic peripheral neuropathic pain

Condition	Intervention	Phase
Posttraumatic Peripheral Neuropathic Pain	Drug: pregabalin	Phase IV

MedlinePlus consumer health information

Study Type: Interventional
Study Design: Treatment, Randomized, Double-Blind, Placebo Control, Parallel Assignment, Efficacy Study

Official Title: A 9 Week, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Study Of Pregabalin (Bid) In Subject With Posttraumatic Peripheral Neuropathic Pain

Further study details as provided by Pfizer:

Primary Outcomes: Weekly Mean Pain Score at Week 8 (or early termination, last observation carried forward [LOCF]) from Daily Pain Diary
Secondary Outcomes: Hospital Anxiety and Depression Scale (HADS) Anxiety sub-scale score
Expected Total Enrollment: 260

Study start: January 2006

Eligibility

Ages Eligible for Study: 18 Years - 80 Years, Genders Eligible for Study: Both

Criteria

Inclusion Criteria:

- Diagnosis of Posttraumatic Peripheral Neuropathic Pain (NeP) syndrome, including post-surgical NeP, NeP due to peripheral nerve injury, and phantom limb pain, confirmed by a qualified pain specialist and persisting for a minimum of 3 months following the traumatic event

Exclusion Criteria:

- Subjects whose posttraumatic neuropathic pain is due to Complex Regional Pain Syndrome (CRPS, Type I or Type II)

Location and Contact Information

Please refer to this study by ClinicalTrials.gov identifier NCT00292188

Pfizer CT.gov Call Center 1-800-718-1021

Belgium
Pfizer Investigational Site, Pellenberg, B-3212, Belgium; Recruiting

Pfizer Investigational Site, Edegem, B-2650, Belgium; Recruiting

Pfizer Investigational Site, Brussels, 1070, Belgium; Recruiting

Pfizer Investigational Site, LiÃ¨ge, B-4000, Belgium; Recruiting

Pfizer Investigational Site, Wilrijk, B-2610, Belgium; Recruiting

Denmark
Pfizer Investigational Site, Hvidovre, 2650, Denmark; Recruiting

Finland
Pfizer Investigational Site, HUS, 00029, Finland; Recruiting

Italy
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Pfizer Investigational Site, Milano, 20127, Italy; Recruiting

Netherlands
Pfizer Investigational Site, Alkmaar, 1815 JD, Netherlands; Recruiting

Pfizer Investigational Site, Breda, 4819 EV, Netherlands; Recruiting

Netherlands, NB

Pfizer Investigational Site, Tilburg, NB, 5022 GC, Netherlands; Recruiting

Romania

Pfizer Investigational Site, BUCURESTI, 021155, Romania; Recruiting

Study chairs or principal investigators

Pfizer CT.gov Call Center, Study Director, Pfizer

More Information

Study ID Numbers: A0081064
Last Updated: March 13, 2006
Record first received: February 13, 2006
ClinicalTrials.gov Identifier: NCT00292188
Health Authority: United Kingdom: Department of Health
ClinicalTrials.gov processed this record on 2006-07-24

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National Institutes of Health, Department of Health & Human Services
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Exhibit "E"

ClinicalTrials.gov, "Study of Pregabalin Versus Placebo in the Treatment of Nerve Pain Associated With HIV Neuropathy," available at http://www.clinicaltrials.gov/ct/show/NCT00232141?order=18 (Accessed: July 24, 2006) (4 pages).

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Study of Pregabalin Versus Placebo in the Treatment of Nerve Pain Associated With HIV Neuropathy

This study is currently recruiting patients.
Verified by Pfizer April 2006

Sponsored by: Pfizer
Information provided by: Pfizer
ClinicalTrials.gov Identifier: NCT00232141

Purpose

Study to determine if pregabalin is more effective than placebo in treating subjects with nerve pain associated with HIV neuropathy.

Condition	Intervention	Phase
Peripheral Neuropathy HIV	Drug: pregabalin Drug: placebo	Phase III

MedlinePlus related topics: Peripheral Nerve Disorders
Genetics Home Reference related topics: Peripheral Nerve Disorders

Study Type: Interventional
Study Design: Treatment, Randomized, Double-Blind, Placebo Control, Parallel Assignment, Safety/Efficacy Study

Official Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multi-Center Trial of Pregabalin Versus Placebo in the Treatment of Neuropathic Pain Associated With HIV Neuropathy.

Further study details as provided by Pfizer:

Primary Outcomes: Comparison of change in mean weekly pain score from baseline to end of study as measured on a daily pain diary on a 11-point rating scale.
Secondary Outcomes: Proportion of subjects experiencing 30 and 50% reduction in pain at endpoint (responder rates); weekly mean pain scores; patient global impression of change; MOS-Sleep Scale; Hopsital Anxiety and Depression Scale; Gracely Pain Scale; Brief Pain Inventory
Expected Total Enrollment: 300

Study start: November 2005

Eligibility

Ages Eligible for Study: 18 Years and above, Genders Eligible for Study: Both

Criteria

Inclusion Criteria:

- Subjects with confirmed diagnosis of HIV infection
- HIV-associated neuropathic pain (nerve pain) for at least 3 months prior to study start
- subjects with moderate to severe pain
- subjects on stable HIV and pain medications (some medications are not allowed to be taken while participating in the study).

Exclusion Criteria:

- Pregnant or breast feeding females
- subjects using street drugs or alcohol abusers during the study
- subject's on anti-diabetic medications
- use of neuroregenerative agents or neurotoxic chemotherapeutic agents 3 months prior to study start and throughout the study
- use of neurotoxic drugs (other than D-drugs) within a month prior to study start and throughout the study.

Location and Contact Information

Please refer to this study by ClinicalTrials.gov identifier NCT00232141

Pfizer CT.gov Call Center 1-800-718-1021

Arizona
Pfizer Investigational Site, Phoenix, Arizona, 85023, United States; Recruiting

Arkansas
Pfizer Investigational Site, Little Rock, Arkansas, 72207, United States; Recruiting

California
Pfizer Investigational Site, San Francisco, California, 94117, United States; Recruiting

Pfizer Investigational Site, Los Angeles, California, 90025, United States; Recruiting

Pfizer Investigational Site, West Hollywood, California, 90069, United States; Recruiting

Colorado
Pfizer Investigational Site, Denver, Colorado, 80262, United States; Recruiting

Florida
Pfizer Investigational Site, West Palm Beach, Florida, 33407, United States; Recruiting

Pfizer Investigational Site, Vero Beach, Florida, 32960, United States; Recruiting

Pfizer Investigational Site, Miami, Florida, 33133, United States; Recruiting

Massachusetts
Pfizer Investigational Site, Boston, Massachusetts, 02215, United States; Recruiting

Pfizer Investigational Site, Springfield, Massachusetts, 01107, United States; Recruiting

New York
Pfizer Investigational Site, New York, New York, 10018, United States; Recruiting

Pfizer Investigational Site, Rochester, New York, 14642, United States; Recruiting

Pfizer Investigational Site, New York, New York, 10029, United States; Recruiting

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Pfizer Investigational Site, Portland, Oregon, 97209, United States; Recruiting

Texas
Pfizer Investigational Site, Dallas, Texas, 75208-4234, United States; Recruiting

Pfizer Investigational Site, Austin, Texas, 78705, United States; Recruiting

Pfizer Investigational Site, San Antonio, Texas, 78229, United States; Recruiting

Washington
Pfizer Investigational Site, Seattle, Washington, 98104, United States; Recruiting

Puerto Rico
Pfizer Investigational Site, Ponce, 00716, Puerto Rico; Recruiting

Pfizer Investigational Site, San Juan, 00909-1711, Puerto Rico; Recruiting

Study chairs or principal investigators

Pfizer CT.gov Call Center, Study Director, Pfizer

More Information

Study ID Numbers: A0081066
Last Updated: April 11, 2006

Record first received: September 30, 2005
ClinicalTrials.gov Identifier: NCT00232141
Health Authority: United States: Food and Drug Administration
ClinicalTrials.gov processed this record on 2006-07-24

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National Institutes of Health, Department of Health & Human Services
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Exhibit "F"

ClinicalTrials.gov, "Trial of Efficacy and Safety of Pregabalin in Subjects With Neuropathic Pain Associated With Lumbo-Sacral Radiculopathy," available at http://www.clinicaltrials.gov/ct/show/NCT00159705?order=19 (Accessed: July 24, 2006) (5 pages).

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Trial of Efficacy and Safety of Pregabalin in Subjects With Neuropathic Pain Associated With Lumbo-Sacral Radiculopathy

This study is currently recruiting patients.
Verified by Pfizer April 2006

Sponsored by: Pfizer
Information provided by: Pfizer
ClinicalTrials.gov Identifier: NCT00159705

Purpose

Trial will evaluate the efficacy and safety of pregabalin in the treatment of subjects with neuropathic pain associated with lumbo-sacral radiculopathy.

Condition	Intervention	Phase
Radiculopathy	Drug: pregabalin	Phase III

MedlinePlus related topics: Peripheral Nerve Disorders
Genetics Home Reference related topics: Peripheral Nerve Disorders

Study Type: Interventional
Study Design: Treatment, Randomized, Double-Blind, Placebo Control, Parallel Assignment, Safety/Efficacy Study

Official Title: A Randomized Placebo-Controlled Trial of the Efficacy and Safety of Pregabalin in the Treatment of Subjects With Neuropathic Pain Associated With Lumbo-Sacral Radiculopathy

Further study details as provided by Pfizer:
Primary Outcomes: Pain measurement
Expected Total Enrollment: 200

Study start: April 2005

Eligibility

Ages Eligible for Study: 18 Years and above, Genders Eligible for Study: Both

Criteria

Inclusion Criteria:

- Pain consistent with a diagnosis of chronic lumbo-sacral radiculopathy due to spinal stenosis or disk herniation.
- Radicular pain must be present for at least 3 months and pain stable for at least 4 weeks.

Exclusion Criteria:

- Surgery for lumbo-sacral radiculopathy within previous 6 months and/or more than one previous spinal surgery for pain-radiculopathy.
- Epidural injection for lumbo-sacral radiculopathy within previous 6 weeks and/or anticipated need for treatment with opioid analgesics, anti-epileptic medications or tricyclic antidepressants to alleviate pain due to lumbo-sacral radiculopathy during the course of the study.

Location and Contact Information

Please refer to this study by ClinicalTrials.gov identifier NCT00159705

Pfizer CT.gov Call Center 1-800-718-1021

Arizona
Pfizer Investigational Site, Phoenix, Arizona, 85023, United States; Recruiting

Florida
Pfizer Investigational Site, Plantation, Florida, 33324, United States; Recruiting

Indiana
Pfizer Investigational Site, Indianapolis, Indiana, 46250, United States; Recruiting

New York
Pfizer Investigational Site, Rochester, New York, 14621, United States; Recruiting

Pfizer Investigational Site, Valley Stream, New York, 11580, United States; Recruiting

Oregon
Pfizer Investigational Site, Portland, Oregon, 97239, United States; Recruiting

Pennsylvania
Pfizer Investigational Site, Allentown, Pennsylvania, 18013, United States; Recruiting

Pfizer Investigational Site, Allentown, Pennsylvania, 18103, United States; Recruiting

Pfizer Investigational Site, Bethlehem, Pennsylvania, 18017, United

States; Recruiting

Belgium

Pfizer Investigational Site, Edegem, B-2650, Belgium; Recruiting

Pfizer Investigational Site, Pellenberg, B-3212, Belgium; Recruiting

Pfizer Investigational Site, Genk, B-3600, Belgium; Recruiting

Pfizer Investigational Site, EEKLO, B-9900, Belgium; Recruiting

Canada, Ontario

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Pfizer Investigational Site, Toronto, Ontario, M9W 4L6, Canada; Recruiting

Pfizer Investigational Site, Hawkesbury, Ontario, K6A 1A1, Canada; Recruiting

Pfizer Investigational Site, Kingston, Ontario, K7L 2V7, Canada; Recruiting

Canada, Quebec

Pfizer Investigational Site, Montreal, Quebec, H3A 2B4, Canada; Recruiting

Pfizer Investigational Site, Fleurimont, Quebec, J1H 5N4, Canada; Recruiting

Germany

Pfizer Investigational Site, Muenchen, 81675, Germany; Recruiting

Pfizer Investigational Site, Goeppingen, 73033, Germany; Recruiting

Pfizer Investigational Site, Duesseldorf, 40225, Germany; Recruiting

Pfizer Investigational Site, Kiel, 24105, Germany; Recruiting

Pfizer Investigational Site, Wiesbaden, 65195, Germany; Recruiting

Pfizer Investigational Site, Nuernberg, 90489, Germany; Recruiting

Pfizer Investigational Site, Bremen, 28329, Germany; Recruiting

Italy

Pfizer Investigational Site, Milano, 20100, Italy; Recruiting

Pfizer Investigational Site, Imperia, 18100, Italy; Recruiting

Pfizer Investigational Site, Napoli, 80126, Italy; Recruiting

Pfizer Investigational Site, Pavia, 27100, Italy; Recruiting

Pfizer Investigational Site, Roma, 00168, Italy; Recruiting

Italy, Pavia
Pfizer Investigational Site, Localita' Cravino, Pavia, 27100, Italy; Recruiting

Spain
Pfizer Investigational Site, GRANADA, 18014, Spain; Recruiting

Pfizer Investigational Site, MADRID, 28006, Spain; Recruiting

Pfizer Investigational Site, SEVILLA, 41071, Spain; Recruiting

Pfizer Investigational Site, Sevilla, 41013, Spain; Recruiting

Pfizer Investigational Site, Valencia, 46014, Spain; Recruiting

Spain, BARCELONA
Pfizer Investigational Site, BADALONA, BARCELONA, 08916, Spain; Recruiting

Sweden
Pfizer Investigational Site, Goteborg, 400 10, Sweden; Recruiting

Pfizer Investigational Site, Stockholm, 182 88, Sweden; Recruiting

Pfizer Investigational Site, Lulea, 972 33, Sweden; Recruiting

Pfizer Investigational Site, Skelleftea, 931 87, Sweden; Recruiting

Pfizer Investigational Site, Lidingo, 181 39, Sweden; Recruiting

Pfizer Investigational Site, Linkoping, 581 85, Sweden; Recruiting

Turkey
Pfizer Investigational Site, Ankara, 06100, Turkey; Recruiting

Pfizer Investigational Site, Istanbul, 34390, Turkey; Recruiting

Turkey, IZMIR
Pfizer Investigational Site, Inciralti, IZMIR, 35340, Turkey; Recruiting

Study chairs or principal investigators

Pfizer CT.gov Call Center, Study Director, Pfizer

More Information

Study ID Numbers: A0081007

Last Updated: April 11, 2006
Record first received: September 8, 2005
ClinicalTrials.gov Identifier: NCT00159705
Health Authority: United States: Food and Drug Administration
ClinicalTrials.gov processed this record on 2006-07-24

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